Scoping Review :Benefits of Zingiberaceae Family in Patients with Cancer

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Abstract

Traditional medicine has begun to be widely used in the treatment and prevention of disease, which is supported by the increasing prevelance of chronic diseases and failure of treatment with modern medicine. Cancer as one of the chronic diseases that causes the most death in the world has begun to change treatment patterns using traditional medicines to minimize side effects that occur, one of which is the Zingiberaceae family. This study was conducted to determine the benefits of the Zingiberaceae family in cancer patients, by reviewing published articles. Articles are searched through the Google Scholar, Pubmed and Scopus databases contained in the Publish and Perish application. The results of this study obtained three Zingiberaceae plants in 13 article that had been clinically testes on cancer patients and met the inclusion exclusion criteria for this study. The three plants are: Zingiber officinale (ginger), Curcuma longa (turmeric), and Boesenbergia rotunda (intersection of keys). Zingiber officinale (ginger) is known to have benefits for cancer patient by reducing nausea and vomiting caused by chemotherapy, while Curcuma Longa (turmeric)and Boesenbergia rotunda (cucumber) are known to reduce the degree of oral mucositis due to radiotherapy.

Keyword : Zingiberaceae; Cancer; Clinical trial; Zingiber Officinale; Curcuma longa; Boesenbergia rotunda

INTRODUCTION

WHO (2020) defines cancer as a malignant tumor or neoplasm, cells that develop abnormally, can spread to other organs and disrupt the organ's actual function. WHO reported that deaths due to cancer in the world in the Global Burden of Cancer in 2020 had reached 9.95 million people with 19.29 million new cases, where Indonesia reported increase new cases of 396.9 thousand people with 234.5 thousand deaths [1,2].

The world organization WHO has recommended the return to use of traditional medicines in the treatment and prevention of disease, which is supported by the increasing prevalence of chronic diseases and the failure of treatment with modern medicines.[3,4] This proves that herbs can be a treatment that is widely accepted and can treat diseases with minimal side effects [5–7]

The Zingiberaceae family or often called the ginger family grows widely in tropical and subtropical areas, especially Indonesia, and has also been widely used, cultivated and utilized as a kitchen spice, medicinal ingredient, cosmetic ingredient, spice, drink, and ornamental plant.[8,9] Several species of Zingiberaceae such as Curcuma zedoaria (white ginger), Curcuma longa (turmeric), Zingiber zerumbet (lempuyang elephant), Curcuma mangga (mango ginger), Zingiber officinale (red ginger) and Zingiber ottensi (ghost ginger) are known to have active substances capable of against cancer.[10–14] Futhermore, Boesenbergia rotunda (Gun Key) is known to have anti-angiogenesis activity for cancer

therapy[15]. Based on this, researchers will conduct research that summarizes all clinical research on Zingiberaceae and its benefits against cancer.

RESEARCH METHODS

This research was conducted Scoping Rivew method to summarizing clinical study and effect of intervention[16,17]. In this scoping review, there are several article selection criteria contained in the inclusion criteria: (1) is clinical research; (2) Articles with Randomized controlled Trials (RCTs); (3) Articles in English and Indonesian also high impact; (4) Mention the management and benefits of Zingiberaceae for cancer; (5) This research from the last 5 years (2017 – 2021), and exclusion criteria: (1)Articles using case studies/case series/case control studies/ cohortstudies/ meta analysis/ systematic review methods.

Article searches in the publish and perish application with the Google Scholar, PubMed and Scopus databases were carried out with the keywords: *"zingiberaceae for cancer OR zingiberaceae OR Curcuma zedoaria for cancer OR Curcuma longa for cancer OR Zingiber zerumbet for cancer OR Zingiber ottensi for cancer OR Boesenbergia rotunda for cancer OR Curcuma mango for cancer OR Zingiber officinale for cancer OR anticancer OR cytotoxic effect OR antitumor OR antimutagenic OR antioxidant AND clinical study OR rct"*

RESULT

A search on the Publish and Perish application (Figure 1) shows a total of 4,415 articles, of which 4,397 articles were from the Google Scholar database, 1 article from the Pubmed database and 17 articles from the Scopus database. The articles had been collected then screened based on the title or abstract and 34 articles were obtained which entered the final stage, to screening the entire of the article. From this final stage, 13 articles were obtained the inclusion-exclusion criteria shown in table 1.1:

DISCUSSION

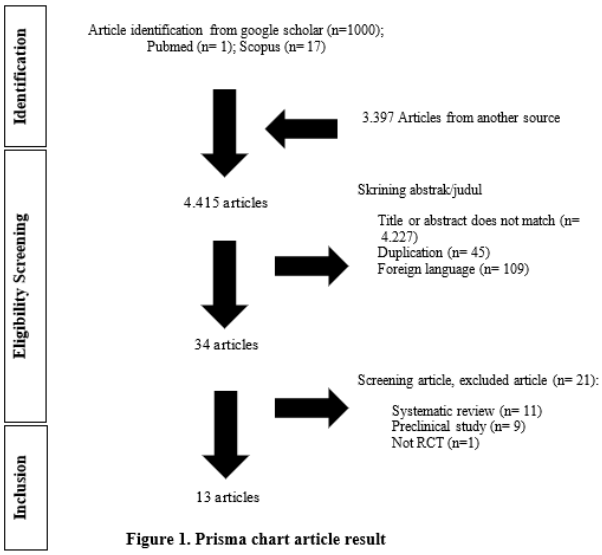

Figure 1. Prisma chart article result

1. *Zingiber officinale*

Based on article, it is known that ginger (Zingiber officinale) was used in seven clinical studies. Two studies were conducted on cancer patients who were divided into two separate groups and given ginger extract and a placebo, then the Functional Living Index-Emesis (FLIE) scores of the two groups were compared. In research by Bossi et al., (2017) and Marx et al., (2017), the results showed that the group given ginger extract got a higher FLIE score than placebo. In the study by Edgham-zamiri et al., (2020) it was conducted on breast cancer patients who were undergoing outpatient chemotherapy before undergoing mastectomy. The results of research using the Rhodes nausea and vomiting assessment scale, it showed that the group given ginger got higher scores than the control. In a study by Sriningsih et al., (2017), post-cervical cancer patients undergoing chemotherapy were divided into groups who were given ginger aromatherapy or placebo while still being given antiemetic drugs. The results of measurements by MASCC (Multinational Association of Supportive Care in Cancer) showed that cervical cancer patients who were given ginger aromatherapy got higher scores than controls.

Danwilai K et al., (2017) research was conducted to determine antioxidant activity in breast cancer patients undergoing chemotherapy. The results showed that the antioxidant activity of cancer patients given ginger extract had a high value compared to controls. In a study by Li et al., (2018), the results of measurements using the MASCC Antiemesis Tool

(MAT) in lung cancer patients did not show a significant difference in the severity of nausea between those given ginger and controls. In a study by Thamlikitkul et al., (2017) conducted on breast cancer patients who took the drugs adrinamycin and cyclophospamide (AC), the results showed that administration of ginger did not reduce nausea and vomiting in the treatment group compared to the control. It can be concluded that ginger can reduce nausea and vomiting caused by chemotherapy in cancer patients and is useful in improving the patient's quality of life.

It is known that the phenols contained in ginger provide anti-oxidative effects which can protect cells from damage, while the gingerols contained in ginger are able to overcome nausea, reduce pain, muscle aches and prevent cancer[18,19]. Based on research by Walstab et al., (2013), it is known that the compounds 6-shogaol, 6-gingerol and zingerone in ginger play a role in suppressing 5-HT receptors in transmitting emetic signals in vagal afferent nerves, thereby preventing the onset of nausea and vomiting[20].

2. Curcuma longa

On article, its known that turmeric (Curcuma longa) was used in five clinical studies of cancer patients receiving chemotherapy with the side effect of oral mucositis. Filho et al., (2018) was conducted on head and neck cancer patients who were divided into two groups to be given a dose of FITOPROT (curcuminoids and Bidens pilosa extract). The results showed that there was no toxicity or adverse side effects from the results of laboratory examinations and clinical conditions. Research by Arun P et al., (2020); Shah S et al., (2020) and Delavarian Z et al., (2019) were conducted on head and neck cancer patients who were undergoing radiotherapy treatment. The results of the study showed that the group given turmeric experienced a mild degree of oral mucositis compared to the control group (Arun et al., 2020). While Delavarian Z et al., (2019) and Shah S et al., (2020) study of nanocurcumin in the treatment group showed that patients experienced a milder degree of oral mucositis than the control group.

Soni et al., (2022) conducted study on oral cancer patients who had undergone radical surgery and had no previous history of radiotherapy. The results of the study showed that the degree of oral mucositis decreased in the group given ginger extract compared to placebo. It can be concluded that turmeric can reduce the severity of oral mucositis due to chemotherapy and radiotherapy in cancer patients.

Curcumin in Curcuma longa has an anti-inflammatory effect by modulating the formation of NF-kB, which is an inactive protein in the cytoplasm that functions to regulate inflammation, immune responses, wound healing, and cell death and function[21]. In addition, turmeric extracts and essential oils contain phenolics which can inhibit the growth of various bacteria, parasites and pathogenic fungi [22,23].

3. Boesenbergia rotunda

Based on the the article, according to research by Kongwattanakul et al., (2022), it is known that the fingerroot (Boesenbergia rotunda) was used in clinical study on cancer patients who received radiotherapy with the side effect of oral mucositis. This research was conducted on head and neck cancer patients who were divided into three groups and given different treatment for each group. The first group was given payayor (Clinacanthus nutans Lindau) mouthwash, the second group was given fingerroot (Boesenbergia rotunda) mouthwash and the third group was given normal saline with sodium bicarbonate as a control. The results of the study showed that administering herbal medicine reduced the severity of RIOM (Radiation-induced Mucositis) but did not reduce the symptoms that appeared, which means that fingerroot is safe to use to reduce the severity of oral mucositis due to radiotherapy.

Flavonoid compounds and essential oils in fingerroot act as antimicrobials to inhibit pathogens, especially pathogens in the mouth, throat, respiratory tract and skin. This antimicrobial activity is carried out by inhibiting or destroying the work of enzymes needed to form bacterial membranes or walls. In certain bacteria such as Streptococcus pyogenes, the compounds in this key ingredient can cause a decrease in enzyme production and activity in the bacteria which results in hydrolysis and haemolysis[24].

LIMITATION

A limitation in this research is that some articles do not explain in detail whether the method used in dividing the groups was random or not.

CONCLUSION

1. Ginger (Zingiber officinale) can reduce nausea and vomiting caused by chemotherapy.
2. Turmeric (Curcuma longa) is safe to use as a mouthwash to reduce the severity of oral mucositis due to chemotherapy.
3. Fingerroot (Boesenbergia rotumda) is safe to use as a mouthwash to reduce the severity of oral mucositis due to radiotherapy.

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Tabel 1. List Scoping Review Articles

No	Country	Article Title	Researcher	Design	Name of plant/compound	Population	Treatment	Results
1.	Italy	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of a Ginger Extract in The Management of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients Receiving High Dose Cisplatin	(Bossi et al., 2017)	Randomized, double-blind, placebo controlled.	Zingiber officinale/ shogaoil and gingerols	Adult patients (≥18 years) with solid tumors and received two cycles of HEC-naive chemotherapy with cisplatin (single dose >50mg/m every 21 or 28 days) (N= 251). The population was divided into treatment groups with ginger (N=125) and placebo (N=126)	The patient is scheduled to receive 2 treatments with ginger extract 160 mg/day. In the first period, ginger extract was given from day 2 to day 21-28, while the second period started from day 23 or day 30 to day 42 or 56.	The treatment of patients with ginger in calculating the Functional Living Index-emesis (FLIE) score was higher than patients with placebo
2.	Australia	The Effect of a Standardized Ginger Extract on Chemotherapy-Induced Nausea-Related Quality of Life in Patients Undergoing Moderately or Highly Emetogenic Chemotherapy: A Double Blind, Randomized, Placebo Controlled Trial	(Marx et al., 2017)	Double-blind, randomized placebo-controlled,	Zingiber officinale/ gingerols and shogaol	Patients were adults (≥18 years), had a Karnofsky score >60, were chemotherapy naïve with a highly emetogenic regimen, and had no neoplasms or diseases that caused nausea, and did not consume products or medications that caused nausea (N=51). Where the population received 1.2g ginger extract treatment (n=24) and placebo (n=27)	All participants filled out a questionnaire after each chemotherapy cycle of the 3 cycles assessed. For each cycle, outcomes were assessed within 7 days (3 days before chemotherapy and 4 days after chemotherapy). The group that received ginger extract consumed ginger extract 4 times per day (4x300mg) for 5 days from the first day of chemotherapy.	Treatment of patients with ginger in calculating the Functional Living Index-emesis (FLIE) score resulted in better results and lower levels of fatigue than patients with placebo.
3.	Brazil	Randomized Clinical Trial of a Mucoadhesive Formulation Containing Curcuminoids (Zingiberaceae) and Bidens pilosa Linn (Asteraceae) Extract (FITOPROT) for Prevention and Treatment of Oral Mucositis – Phase I Study	(Filho et al., 2018)	Randomized, double-blind,	Curcuma longa/ curcuminoids	20 patients with an age range of 19–46 years, received chemotherapy which caused oral mucositis in head and neck cancer patients.	Treatment was carried out in 2 groups, group 1 (FITOPROT A) was given 10 mg of curcuminoids extract and 20% Bidens pilosa extract, while group 2 (FITOPROT B) was given 20 mg of curcuminoids extract and 40% Bidens pilosa extract which was done by gargling 3 times a day for 10 days.	There was no excessive and detrimental toxicity or side effects found in laboratory and clinical examinations in the normal condition of the trial participants.
4.	China	Efficacy of Ginger in Ameliorating Acute and Delayed Chemotherapy-Induced Nausea and Vomiting Among Patients With Lung Cancer Receiving Cisplatin-Based Regimens: A Randomized Controlled Trial	(Li, X; Qin, Y et al., 2018)	Randomized, double-blind, placebo controlled.	Zingiber officinale/ gingerols	146 patients with lung cancer who were allocated placebo (n=73) and received 1 g ginger extract treatment (n=73)	Treatment is carried out by giving the first dose of treatment 30 minutes before chemotherapy on the first day. Each group was given 0.5 g 2 capsules per day for the ginger group and 0.25 g per capsule every 12 hours for 5 days.	As an additional therapy for antiemetics, ginger is not efficient in improving chemotherapy-induced nausea and vomiting in lung cancer patients receiving cisplatin therapy by measuring the MASCC Antiemesis Tool (MAT).
5.	Thailand	Efficacy of Ginger For Prophylaxis of Chemotherapy-Induced Nausea and Vomiting In Breast Cancer Patients Receiving Adriamycin–Cyclophosphamide Regimen: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study	(Thamlikitkul et al., 2017)	Randomized, double-blind, placebo-controlled, crossover study	Zingiber officinale/ gingerols	Breast cancer patients who received adriamycin and cyclophosphamide (AC) therapy and showed symptoms of nausea and vomiting since the first cycle of chemotherapy (n= 34)	During the second cycle of chemotherapy, 19 patients were treated with 500 mg of ginger 2 times per day for 5 days, while 15 other patients were given placebo. Then in the third cycle, patients who received treatment with ginger were given a placebo and patients who received a placebo were given 500 mg of ginger.	34 patients with a total of 68 AC cycles who received ginger and placebo treatment alternately in the second and third cycles of chemotherapy, found that 500 mg of ginger consumed twice a day was safe to use, but did not provide significant benefits for reducing nausea and vomiting in cancer

							All patients were still given ondansetron and dexamethasone as prophylaxis to reduce nausea and vomiting caused by chemotherapy.	patients. breasts that consume AC, ondansetron and dexamethasone.
6.	Iran	Effects of ginger capsules on treatment of nausea and vomiting in patients receiving cisplatin undergoing mastectomy: a randomized clinical trial	(Eghdam-zamiri, 2020)	Randomized clinical study	Zingiber officinale/ gingerols	60 breast cancer patients undergoing treatment at the chemotherapy clinic at Tabriz Shahid Madani Hospital in 2018-2019.	Patients were divided into intervention and control groups. The intervention group was given 500 mg ginger tablets 2 times a day, starting from 10 days after chemotherapy until one week before mastectomy, while the control group was given placebo tablets. The patient's nausea and vomiting score was assessed before the intervention and after the mastectomy.	The results of the study showed differences in nausea and vomiting scores in the treatment group after the intervention, while there were no significant differences in the control group of patients. So it can be concluded that ginger is effective in treating nausea and vomiting in women who take cisplatin and will undergo a mastectomy.
7.	Indonesia	Aromatherapy ginger use in patients with nausea & vomiting on post cervical Cancer chemotherapy	(Sriningsih et al., 2017)	Clinical study, pre and post control group design	Zingiber officinale/ ginger essential oil	60 patients at Dr. Moewardi Surakarta who is undergoing chemotherapy after cervical cancer. Participants were then divided into the intervention group (n = 30) and the control group (n = 30)	Both groups were still given the same chemotherapy (cisplatin and 5-fluorouracil) and antiemetic drugs (ondansetron and dexamethasone). The treatment was carried out by giving 5 drops of ginger oil for 10 minutes using a hood mask to the intervention group. Ginger aromatherapy is given twice a day or can be repeated 30 minutes before eating or when feeling nauseous. Assessment of nausea and vomiting was carried out 24 hours before and after aromatherapy was given in the intervention group, and assessed 24 and 48 hours after chemotherapy in the control group.	The results of the study showed a significant difference in nausea and vomiting before and after being given aromatherapy in the intervention and control groups, where there was no significant difference in nausea and vomiting in the control group. Thus, it can be said that ginger aromatherapy can be used as an alternative treatment to reduce nausea and vomiting after chemotherapy.
8.	German	Prophylactic management of radiation-induced mucositis using herbal mouthwash in patients with head and neck cancer: an assessor-blinded randomized controlled trial	(Kongwattanakul et al., 2022)	Randomized clinical trial	Boesenbergia rotunda/ -	120 head and neck cancer patients undergoing radiotherapy were divided into three treatment groups. Each group was given a different mouthwash used during radiotherapy and assessed the degree of mucositis that occurred from the first to six weeks of radiotherapy and the following month.	The treatment group was divided into three groups consisting of the payayor (Clinacanthus nutans Lindau) mouthwash group, the fingerroot (Boesenbergia rotunda) mouthwash group, and the control group which was given normal saline with sodium bicarbonate. Body mass index (BMI) is also assessed as a comparison of nutritional status.	The results of this study show that the 2 mouthwashes have the same effect in reducing the severity of RIOM (Radiation-induced Mucositis), both mouthwashes reduce the symptoms that arise from RIOM but it is not statistically significant, there is also no difference in body mass index between the three groups.
9.	India	Role of Turmeric Extract in Minimizing Mucositis in Patients Receiving Radiotherapy for Head and Neck Squamous cell cancer: A	(Arun P et al., 2020)	Randomized, Single-blinded clinical study	Curcuma longa/ curcuminoids	61 patients who were undergoing radiotherapy treatment for head and neck cancer. The population was divided into Groups A and B, where Group A (n=30)	Turmeric extract was given to Group A at 500 mg three times a day after meals, while Group B was given a placebo three times a day. This treatment is consumed from the first	In the first two weeks of treatment, both groups experienced the same degree of mucositis. Then in the fourth week of treatment, Group B (control) experienced severe

		Randomised, Placebo-Controlled Trial				received treatment with turmeric and Group B (n=31) with placebo.	day of radiotherapy until the radiotherapy treatment is finished.	mucositis with 4 patients experiencing grade 3 mucositis, while Group A experienced mild mucositis (grade 1).
10.	Iran	Oral Administration of Nanomicelle Curcumin in the Prevention of Radiotherapy-Induced Mucositis in Head and Neck Cancers	(Delavarian Z et al., 2019)	Double-blind randomized clinical trial	*Curcuma longa*/ curcuminoids-nano curcumin	32 head and neck cancer patients who were undergoing radiotherapy were divided into a study group (n= 16) and a control group (n= 16).	Patients in the study group were given 80 mg/day of nanocurcumin orally, while the control group were given tablets containing lactose, both of which were consumed for 6 weeks starting from the first day radiotherapy started.	There was a significant difference between the severity of mucositis in the control group and the study group. Where in the control group all patients experienced oral mucositis, while in the study group only 32% of patients experienced oral mucositis.
11.	Thailand	Antioxidant Activity of Ginger Extract as a Daily Supplement in Cancer Patients Receiving Adjuvant Chemotherapy: A Pilot Study	(Danwilai K et al., 2017)	Pilot, randomized, double-blind, placebo-controlled trial	*Zingiber officinale*/ gingerol	Patients aged ≥18 years who were confirmed to have a tumor and had the entire tumor removed, and received ≥ 3 cycles of adjuvant emetogenic chemotherapy. The population consisted of 50 female patients, all of whom suffered from breast cancer and were divided into two groups, namely the treatment group (n= 25) and placebo (n= 25).	Treatment was carried out by giving 5mg 6-gingerol capsules or 2 placebo capsules twice a day according to the treatment group, starting from three days before the first cycle of chemotherapy until the fourth cycle of chemotherapy.	There was a significant difference in the increase in antioxidant activity and reduction in oxidative marker levels in patients who received gingerol treatment compared to patients who received placebo.
12.	India	Effectiveness of Curcumin Mouthwash on Radiation-Induced Oral Mucositis Among Head and Neck Cancer Patients: A Triple-Blinded, Pilot Randomized Controlled Trial	(Shah S et al., 2020)	Triple-blinded, pilot randomized controlled trial	*Curcuma longa*/curcumin nanoparticles	74 patients who were confirmed to have squamous cell carcinoma of the head and neck, were scheduled for radiotherapy for 6-7 weeks, and had a Karnofsky score≥ 70 %	The experiment was carried out by randomly dividing participants into 2 groups, and given a mouthwash bottle containing benzidamine (0.15%) as a control and a mouthwash bottle containing curcumin (0.1%) as an experiment. Patients were asked to use 10 mL of mouthwash three times a day for 7 days without mixing with water and were evaluated every week.	Based on RIOM (Radiation-Induced Oral Mucositis) which was assessed in both groups, the results showed that all participants experienced oral mucositis. However, the degree of mucositis experienced by patients given curcumin was milder compared to controls.
13.	India	A Randomized, Placebo-Controlled Study to Evaluate the Effect of Bio-Enhanced Turmeric Formulation on Radiation-Induced Oral Mucositis	(Soni et al., 2022)	*Randomized, double-blinded, three-arm trial*	*Curcuma longa*/curcuminoids	A total of 60 oral cancer patients who had undergone radical surgery (wide excision with modified neck dissection), were aged 18 – 70 years, without a history of previous radiotherapy to the head and neck area and were willing to fill out an informed consent form.	The entire population was divided into 3 groups (A, B, C) with different interventions. Group A was given 500 mg Bio-enhanced turmeric formulation (BTF) taken 2 times a day; Group B was given 500 mg Bio-enhanced turmeric formulation (BTF) taken 3 times a day; while Group C was given placebo 3 times a day, all of which was taken during 6 weeks of radiotherapy.	The results showed that grade 3 oral mucositis, oral pain, dysphagia and dermatitis were significantly reduced in patients who received BTF rather than placebo. BTF can significantly reduce chemoradiotherapy-induced severe oral mucositis, dysphagia, oral pain and dermatitis in oral cancer patients.